REMARKS

Claims 1-16 are pending in the Application. Claim 1 has been amended. Claims 10-16 are newly added. Claim 1 has been amended to even more clearly recite certain salient features of the optical illumination system. In particular, claim 1 has been amended to recite that a moving optical gradient field is used to cause the selective separation of at least a portion of the particles away from the first surface. In addition, claim 1 has been amended to recite the feature that the second adhesive surface adheres at least a portion of the separated particles.

Applicants' Invention

The present invention is directed to devices and methods for the collection and sorting of particles. Particles may comprise biological materials such as cells, organelles, proteins, and the like or even non-biological materials. Sorting and collection of particles is performed using a moving optical gradient field that can selectively cause the separation of particles away from a first surface. All or a portion of these particles can then be collected by the use of a second adhesive surface.

The claimed invention provides several benefits over other prior art devices and methods. For example, the claimed device and method permits the sorting and collection of particles such as cells without the need for dyes, labels, and other markers. The present device and method therefore avoids the significant costs and added complexity associated with the use of dyes and labels in sorting/collection assays. In addition, when dyes, labels, or markers are used, these materials necessarily affect the particle to which they are bound. Consequently, any subsequent analysis or observation of the particle(s) is in some

sense tainted by the presence of the label or marker. In many applications, such as the collection and sorting of live cells, it is preferable and indeed imperative to retain the cell in its native, unlabelled state. The present invention, for example, permits the sorting and collection of unlabelled, physiologically normal, intact cells.

The present invention also permits the selective separation of particles based on fundamental properties of the particle itself. For instance, with respect to particles such as cells, each cell has its own Optophoretic signature which uniquely reflects the physiological state of the cell at the exact moment in which it is being analyzed. The present invention capitalizes on this observation by using a moving optical gradient field to sort and collect particles based on their different Optophoretic signatures. The device has numerous practical applications particularly for applications in the biological field. For example, Applicants' claimed apparatus and method allow the simple and efficient gathering of a wide spectrum of information, from screening new drugs, to studying the expression of novel genes, to creating new diagnostic tools that are able to detect and monitor disease states such as cancer.

Prior Art Rejections

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Publication No. 2002/0058332 A1 (Quake et al.) in view of U.S. Patent No. 6,399,397 (Zarling et al.). This rejection is respectfully traversed.

Quake et al.

Quake et al. discloses a microfluidic device for analyzing and sorting of biological materials. Figures 14(a) and 14(b) of Quake et al. illustrate a microfluidic sorting device

that includes an input channel, a waste channel, and a collection channel. A "T" intersection is formed at the intersection of these three channels. In one embodiment, Quake et al. purports to describe a method of sorting particles through the use of an optical trap or laser tweezer. ¶ 240. In the Quake et al. device, a detection region is provided upstream of the optical trap in the input channel that "detects" the presence or absence of a particle of interest. ¶ 240; see also Figs. 14(a) and 14(b) showing detection window. Detection of the particle of interest is accomplished by detecting or optically measuring the presence or amount of marker or reporter that is bound to the particle. ¶ 69 (definition of "detection region").

Different pressure gradients are established in the waste channel and the collection channel. ¶ 240. A larger gradient at one branch channel creates a dominant flow of particles into the waste channel. Id. A second, smaller gradient at another branch channel is used to create a slower flow of fluid that directs particles into the collection channel. Id. The optical trap or tweezers are in the "off" mode until a desired particle is detected at the detection region by the measured amount of light or fluorescence. Id.; see also ¶ 235. When the particle of interest is detected, the optical trap is turned on so as to trap the particle. ¶ 240. The particle is then directed or moved into the collection channel. The laser trap is turned off to release the particle into the collection chamber. Id.

There are several differences with the device and methods employed by Quake et al. and the claimed device and method found in the present Application. The first difference relates to the use of the Quake et al. laser trap vs. Applicants' claimed optical illumination system. In Applicants' claimed apparatus, the plurality of particles are subject

to a moving optical gradient field that causes the selective separation of at least a portion of the particles away from the first surface. The selective separation of the particles in the claimed invention is due to the interaction of the moving optical gradient field with the individual particles. In particular, when the plurality of particles is interrogated with the moving optical gradient field, some particles having a certain Optophoretic signature will remain disposed adjacent to the first support surface (i.e., see particles 454 and 452 in Fig. 22 of Applicants' specification) while other particles having different Optophoretic signatures will move away from the first surface (i.e., particles 458 and 456). Thus, some particles, based on their Optophoretic signatures, will remain in place even when they are subject to the moving optical gradient field.

In contrast, in the Quake et al. device and method, every particle that encounters the laser trap (when turned on) will be trapped. The laser trap itself provides absolutely no selectivity. Instead, Quake et al. relies on a separate detector region that is used to identify and select those desired particles based on their light or fluorescence readings. Unlike the Quake et al. device, Applicants' claimed moving optical gradient field imparts motion to the particles as well as "selects" which particles move based on their Optophoretic signatures. In Applicants' claimed device there simply is no need for a separate "detector" for selecting which particles to move.

In addition, there is a significant difference between Applicants' claimed moving optical gradient field which interrogates a plurality of particles so as to selectively separate at least a portion of the interrogated particles and Quake et al.'s optical trap which neither interrogates a plurality of particles nor selectively separates a portion of the interrogated

particles. As stated in detail above, the optical trap of Quake et al. traps only a single particle of interest and only after the particle of interest was detected upstream in a detection region by the amount of light emitted from a marker attached to the particle. Quake et al.'s optical trap does not interrogate a plurality of particles at the same time, nor does the optical trap allow the selective separation of particles as a result of their interaction with the moving optical gradient.

Finally, as acknowledged in the Official Action, Quake et al. fails to disclose the use of an adhesive surface for adhering separated particles. Applicants submit, however, that Quake et al. also fails to disclose or otherwise suggest the claimed first surface that is adapted to support a plurality of particles. Quake et al. concerns a microfluidic sorting device that includes multiple microchannels through which the particles travel. Droplets of solution containing the biological material are deposited into a main channel and a fluid different from and incompatible with the solution containing the biological material flows through the main channel so that the droplets containing the biological material do not diffuse or mix. In this regard, there is no surface on which the plurality of particles are supported – the particles are always contained within immiscible droplets flowing within the lumen of the microchannel.

Zarling et al.

Zarling et al. discloses an up-converting reporter system for use in biological and other assays using laser excitation techniques. As stated in Zarling et al., the invention "provides the use of *luminescent materials* that are capable of multiphoton excitation and have upshifted emission spectra." Col. 5, lines 46-48 (emphasis added). Applicants note

that the Zarling et al. assays are specifically directed at the use of luminescent labels and markers – something that the present claimed invention attempts to avoid.

Fig. 29 of Zarling et al. discloses a hand-held probe that uses the up-converting reporter system. The hand-held probe has a housing D1 and a capillary wick D2. The housing also includes, among other things, a diode excitation laser D3, a lens assembly D4, and a photodiode detector D5. Col. 39, lines 1-4. During use, the wick D2 wicks up a portion of sample fluid D8 which is suspected of containing target antigens. Col. 39, lines 8-9. The lower portion of the wick D2 is impregnated with upconverting phosphors (i.e., labels) that are conjugated to the target analyte or a cross-reactive epitope for the capture probe. Col. 39, lines 25-28. The phosphors work their way towards the capture surface D9 as sample fluid is drawn up the wick D2. Col. 39, lines 28-30. As the phosphors accumulate at the capture surface D9, they will begin to emit visible light upon excitation by the laser D3 which is then detected by the detector D5. Col. 39, lines 30-34.

§ 103(a) Rejection

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Quake et al. in view of Zarling et al. According to the Office Action, it would have been obvious to one of ordinary skill in the art that the Quake et al. optical trapping apparatus and method could have been modified to use of the analyte detection technique disclosed in Zarling et al. Applicants traverse this rejection.

Applicants point out that even if the teachings of Zarling et al. are combined with the teachings found in Quake et al., the claimed apparatus could not be produced. Specifically, claim 1 as currently amended recites the feature of an optical illumination system that

subjects particles to a moving optical gradient field to cause selective separation of the particles. As stated in detail above, the device of Quake et al. does not use a moving optical gradient to provide selective separation of particles. Rather, Quake et al. uses a light detecting system to identify particles of interest. The optical trap disclosed in Quake et al. is used as a transport mechanism to deliver the particle of interest to a collection chamber. The laser trap does not perform any selective separation of the particles. Every particle that comes into contact with the laser trap is trapped – there is no selective separation.

In addition, Applicants' claimed apparatus interrogates a plurality of particles with a moving optical gradient field. Selective separation is effectuated based on an individual particle's interaction with the moving optical gradient field. During interrogation, some particles remain disposed on a first surface while others move away from the first surface (i.e., toward the second adhesive surface). In Quake et al., however, a single particle of interest is "trapped" within the optical trap. In Quake et al. trapping is performed on a particle-by-particle basis and only after a separate detector is used to identify those particles of interest.

Applicants also submit that neither Quake et al. nor Zarling et al. discloses or otherwise suggests the claimed first surface that is adapted to support a plurality of particles. In Quake et al., particles are disposed within droplets of fluid contained within the lumen of microchannels. There is no surface supporting particles. Similarly, there is no glass surface supporting particles (e.g., dependent claim 6). In Zarling et al., the target antigens are contained in a sample solution. See, e.g., Fig. 29.

Applicants also disagree with the assertion made in the Official Action that the claimed apparatus could be produced by adding the wicking and capture surface D9 features found in Zarling et al. to the device of Quake et al. Even assuming, *arguendo*, that Quake et al. discloses each claimed element in independent claim 1 but for the second adhesive surface, there would be no motivation or suggestion to combine the teachings of the large hand-held device of Zarling et al. to the microfluidic apparatus of Quake et al. First, the Zarling et al. device concerns a relatively large, hand-held probe that uses a capillary wicking force to deliver target analytes a relatively long distance from a sample to the capture surface D9 for subsequent imaging. The Quake et al. device, in contrast, is a small-scale microfluidic device that sorts particles by movement over relatively small distances. Quake et al. relates to microfluidic sorting technologies while Zarling et al. concerns a device used to detect and measure light emitted from labeled targets in response to illumination from laser light. Quake et al. and Zarling et al. are thus non-analogous art.

Finally, the teachings of Quake et al. are inconsistent with adding a capture surface D9 such as that disclosed in Zarling et al. In Quake et al., the particles of interest are contained within droplets of solution that are immiscible in a fluid passing through the channels of the device. Quake et al. teaches that the material chosen for the fluid should be one such that the droplets containing the biological material do not diffuse or mix. With this in mind, even if a capture surface D9 were added to the Quake et al. device, the capture surface would fail to capture the biological material contained within the droplets since the biological material would be sequestered away from the capture surface D9 due

to the immiscible nature of the liquids used. Consequently, a device that combined the features as suggested in the Official Action would render the capture surface inoperable.

The Official Action also states that the claimed feature of dependent claim 9, namely, that the fluid has an index of refraction which is between the indices of refraction of the particles is disclosed or otherwise suggested in Quake et al. Applicants disagree. Quake et al. discloses that radiation pressure can be used to sort objects whose index of refraction is lower than that of the surrounding medium. ¶ 241. Quake et al. does not, however, disclose the claimed feature wherein the index of refraction of the fluid is between the indices of refraction of the particles (i.e., some particles have a lower index of refraction vis-à-vis the fluid while other particles have a higher index of refraction vis-à-vis the fluid).

Applicants submit that the claims are allowable over the art of record. A notice of allowability is respectfully requested.

Respectfully submitted,

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